REMARKS

The foregoing amendments and the following remarks are submitted in response to the communication May 20, 2005.

The Examiner has objected to the Specification because it contains sequence disclosures encompassed by the definitions of nucleotide and/or amino acid sequences, but without Sequence identifiers. Specifically, he cites sequences found at page 74, line 13. Applicants have above amended the Specification to incorporate the corresponding SEQ ID number SEQ ID NO: 4 on page 74 as requested by the Examiner.

Status of the Claims

Claims 1-17 are pending and under examination in the application. Claims 18-33, which are withdrawn from consideration, have been canceled. Claim 4 has been cancelled without prejudice. Claims 1, 3, 8, 9, 10, 11, 13, 14, 15 and 16 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims can be found generally through Applicants' specification.

Claim Objections

Claims 1-17 are objected to because the Examiner requests that "MST1" be spelled out in the first instance of its use. Applicants have corrected claim 1 accordingly and request this objective be withdrawn.

The Specification Fully Enables the Claimed Invention

The Examiner has rejected claims 1-17 under 35 U.S.C. 112, first paragraph, because the Examiner asserts that the Specification does not enable any person skilled in the art to which it pertains, or with which it is most connected, to make and use the invention commensurate in scope with these claims. With regard to Claims 1-17, the Examiner states that the Specification, while being enabling for a method of treating cardiac disease in a mammal comprising administering an effective amount of a compound selected from a dominant negative Mst1 (K594) and XIAP does not reasonably provide enablement for such method comprising administering a compound or agent that blocks or otherwise inhibits Mst1 or Mst1 pathway. The

Examiner cites the Wands factors and determines that undue experimentation is required. Applicants respectfully disagree. Applicants have above amended claims 1, 3, 8, 9, 10, 11, 13, 14 and 15 in order to clarify the language of the claims and to direct the claims more particularly to the invention and to uses of inhibitors of Mst1. The Specification describes and details the effectiveness of Mst1 inhibitors, including a dominant negative mutant of Mst1 and a chemical agent XIAP. In addition, the Specification, at page 54 paragraph [0158], describes that phosphorylation regulates (activates) Mst1 activity and that a C-terminal inhibitory domain of Mst1 affects Mst1. Applicants assert that the skilled artisan can readily identify compounds or agents, including other Mst1 dominant negative mutants and specific Mst1 inhibitors, and can test their ability to inhibit endogenous Mst1 and to thereby modulate cardiac myocyte apoptosis or function, for use in the claimed methods. While experimentation is necessary, it is not undue and well within the capability of the skilled artisan, particularly taking into account the teaching of the Specification and the knowledge publicly available regarding Mst1.

In view of the foregoing remarks and amendments, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph may properly be withdrawn.

Claim Rejections – 35 U.S.C. §102

Claims 1-6, 8-10 and 13-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamamoto et al., 2001, which the Examiner states teaches that cardiac myocytes were transfused with adenoviral vector harboring XIAP (X-linked inhibitor of apoptosis protein) and that overexpression of XIAP abolished morphological changes, increases in DNA fragmentation, activation of caspase-3 and myocyte death caused by chelerythrine. Further, the Examiner remarks, Yamamoto et al. teaches that intravenous injection of chelerythrine activates caspases and promotes apoptosis in adult rat hearts *in vivo*. The Examiner argues that Yamamoto teaches all the elements of claims 1-6, 8-10 and 13-14. Yamamoto does not teach or describe anything with regard particularly to Mst1. Anticipation is a question of fact. Applicants have above cancelled claim 4 and amended claims 1, 3, 8, 9, 10, 13 and 14 in order to clarify the language of the claims and to direct the claims more particularly to the invention and to uses of specific inhibitors of Mst1. Applicants assert that the above amendments obviate this rejection.

The Examiner rejects claims 1-15 under 35 U.S.C. 102(b) as anticipated by Han et al., U.S. Patent No. 6,225,288, which discloses pharmaceutical compositions comprising compounds of formula I useful as inhibitors of caspase-3, which is implicated in modulating apoptosis. Han further teaches, it is asserted, that the compounds are useful to treat, prevent or ameliorate in mammals, especially humans, diseases including cardiac and cerebral ischemia/reperfusion injury (e.g. stroke). The Examiner argues that Han et al teach all the elements of claims 1-15. Anticipation is a question of fact. Han does not teach or describe anything with regard particularly to Mst1. Applicants have above cancelled claim 4 and amended claims 1, 3, 8, 9, 10, 11, 13, 14 and 15 in order to clarify the language of the claims and to direct the claims more particularly to the invention and to uses of inhibitors of Mst1. Applicants assert that the above amendments obviate this rejection.

Claims 1-3, 7-9 and 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Laugwitz et al., U.S. Patent Publication No. 2003/0130216. Laugwitz et al. relates to the use of inhibitor of caspase-3 or caspase-activated deoxyribonuclease (CAD) for the prevention or treatment of cardiac disease, particularly insufficiency of the left ventricle. The Examiner argues that Laugwitz et al teach all the elements of claims 1-3, 7-9 and 13-14. Laugwitz does not teach or describe anything with regard particularly to Mst1. Anticipation is a question of fact. Applicants have above cancelled claim 4 and amended claims 1, 3, 8, 9, 13 and 14 in order to clarify the language of the claims and to direct the claims more particularly to the invention and to uses of inhibitors of Mst1. Applicants assert that the above amendments obviate this rejection.

In view of the foregoing remarks and amendments, Applicants submit that the Examiner's rejections under 35 U.S.C. 102 may properly be withdrawn.

Claim Rejections – 35 U.S.C. §103

Claims 10-12 are rejected under 35 U.S.C. 103(a) as unpatentable over Han et al., U.S. Patent No. 6,225,288, in view of Danilewicz et al., U.S. Patent No. 4,975,444. Danilewicz et al. teach a series of cycloalkyl-substituted glutaramide derivatives which are antihypertensive agents having utility in treatment of cardiovascular disorders and able to inhibit angiotension converting enzyme. Danilewicz teaches that the compounds may be co-administered with other agents for

treatment of cardiac conditions. The Examiner argues that it would have been obvious to the skilled artisan at the time the invention was made to combine Han et al. and Danilewicz et al. Applicants respectfully disagree. As noted above Han et al discloses pharmaceutical compositions comprising compounds of formula I useful as inhibitors of caspase-3, which is implicated in modulating apoptosis, but does not describe or teach anything with regard particularly to Mst1. The combination of Han and Danilewicz does not teach or suggest the use or combination of specific Mst1 inhibitors with any other compounds for treatment of cardiac disease. In particular and in view of the above claim amendments, particularly in claims 10 and 11, the combination of Han and Danilewicz does not make obvious the claimed invention.

Claims 11-17 are rejected under 35 U.S.C. 103(a) as unpatentable over Han et al., U.S. Patent No. 6,225,288 in view of Kukreja, U.S. Patent Publication No. 2004/0009957. Kukreja teaches exposing cells, tissues, organs to a phosphodiesterase-5 (PDE-5) inhibitor to prevent or decrease apoptosis or necrosis prior to, after or during an ischemia/reperfusion event. Further, Kukreja teaches administration of PDE-5 inhibitors to patients undergoing treatment with Doxorubicin to prevent or lessen Doxorubicin-induced cardiotoxicity. The Examiner asserts it would have been obvious to co-administer an inhibitor of Mst1 with Doxorubicin to reduce Doxorubicin-induced cardiotoxicity as taught by Han et al. and Kukreja et al. Applicants disagree. As noted above Han et al discloses pharmaceutical compositions comprising compounds useful as inhibitors of caspase-3, which is implicated in modulating apoptosis, but does not describe or teach anything with regard particularly to Mst1. The combination of Han and Kukreja does not teach or suggest the use or combination of specific Mst1 inhibitors with any other compounds for treatment of cardiac disease. In particular and in view of the above claim amendments, particularly in claims 11, 13, 14 and 15, the combination of Han and Kukreja does not make obvious the claimed invention.

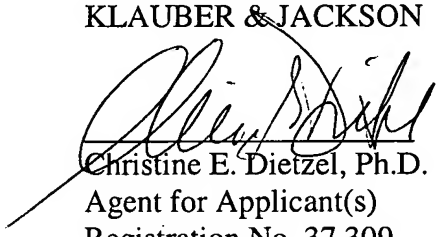
In view of the foregoing remarks and amendments, Applicants submit that the Examiner's rejections under 35 U.S.C. 103 may properly be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

KLAUBER & JACKSON



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